

## **REMARKS**

In response to the Office Action of August 11, 2004 and remaining pending claim 18 the following remarks are presented. As the Examiner is aware, a Restriction Requirement was made in the parent case by the Examiner on March 8, 1999 and at that time original claims 1-17 were elected for prosecution by the Applicants. Applicants acknowledge the Examiner's renumbering of submitted claim 36 under Rule 126 to become claim 18. Applicants will therefore refer to claim 18 only. The pending claim is drawn to a method of creating a fusion protein including an active moiety and was derived from originally filed claim 9. No new claims are added. Claim 18 has been amended.

It is Applicants' position that the amended claim reflects the comments of the Examiner and is in condition for allowance. Reconsideration of this case, as amended, is respectfully requested. No new matter has been added.

## **Specification**

The appropriate SEQ. ID. Numbers, and replacement pages 23 and 39 are provided herein in compliance with 37 CFR 1.821-1.825 and with the Examiner's concerns. Both a clean version of the amended pages, as well as a marked up version are submitted herewith as per 37 CFR § 1.125.

## **Nucleic Acid and/or Amino Acid Sequences**

Applicants have attempted to correct the deficiencies in the specification by adding the appropriate SEQ. ID. Numbers. The sequences are present in the paper copy and CFR of the Sequence Listing filed in this application on February 13, 2004 and it is Applicant's understanding that the paper copy and CFR of the Sequence Listing previously filed complies with the requirements of 37 CFR §§ 1.821(f) and (g); and 1.824. As a result, a new paper and CFR Sequence Listing are not submitted together with amended pages 23 and 39 of the specification.

### **Rejection Under 35 U.S.C. §103**

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hyttinen *et al.*, in view of Copley *et al.* Given the amendment to the pending claim it is Applicants' position, respectfully that the prior rejections are traversed. Reconsideration of amended claim 18 under 35 U.S.C. § 103(a) is, respectfully, requested.

*Copley et al.*,

Copley *et al.* disclose producing fusion proteins and various antibody constructs. It should be noted that claim 18 has been amended to recite a milk specific promoter and a related signal sequence. This is not taught by Copley *et al.* Moreover, as provided on pages 27-30 of the specification these milk specific promoter and signal sequences are important for enhancing the production levels of a protein of interest. This particularly true where one of the moieties claimed is normally a non-secreted protein (carboxypeptidase). Essentially the milk specific promoter and signal sequence recited in the claim will act in part to drive expression in a whole animal transgenic system in a fashion not seen in cell culture systems and not seen in transgenic systems where these sequences are not built into the construct. This also will drive production levels of a desired protein to a higher level on a grams/liter production calculation offering an additional difference with Hyttinen *et al.* and a clear improvement over the cited prior art. Therefore, the amended claim respectfully traverses the remaining rejection.

To this point, and as noted by the Examiner, Copley offers no teachings relative to an appreciable production of a protein of interest (Office Action 8/11/04, page 4). This is not corrected by Hyttinen *et al.*

Given these remarks, reconsideration of the Examiner's rejection of claim 18 under 35 U.S.C. § 103(a) is, respectfully, requested.

*Hyttinen et al.*

Hyttinen *et al.*, does not provide what Copley *et al.*, lacks and moreover is unavailable for combination as seen below. As previously stated, the Hyttinen *et al.* reference essentially

teaches away from the current invention in that it teaches the production of a less active or inactive protein as part of a fusion protein in milk. Specifically, Hyttinen et al. states that polypeptides (such as enzymes) are produced “as fusion proteins that are less active than said biologically active polypeptide in its free form, or non-active. The activity is diminished or removed by having the biologically active polypeptide produced as a fusion protein” (column 2, lines 41-44). This indicates that a critical teaching of the Hyttinen et al., citation is the purposeful production of a biologically inactive molecule. Pending claim 18 recites “biologically active.”

Given this it is respectfully pointed out that nothing in Hyttinen et al. teaches or suggests that an enzyme produced as part of a fusion protein would be in its biologically active form. This is clear from the teachings of Hyttinen et al. which explicitly state that the polypeptide should be inactive or have a diminished biological activity compared to the polypeptide in its free form (emphasis added). Hyttinen et al. further states, at column 4, lines 52-55, that the fusion protein includes a “recombinant DNA encoding a fragment or intact milk or non-milk protein [to provide] the other part of the fusion protein. This polypeptide is used **specifically** to reduce the biological activity of the polypeptide” (emphasis added).

Going further, the teachings of Hyttinen et al. itself make expressly critical that the production of protein must provide inactive molecule since “[s]evere side effects are ... probable when producing potent polypeptides like growth factors, cytokines or enzymes.. “ See column 2, lines 23-24. This is a far cry from the claimed invention which requires that the second member- the enzyme portion- of the fusion protein be produced in its biologically active form. Thus, the teachings of Hyttinen et al. are not just far afield of what the current claim recites, they actually teach away from the claimed invention. More to the point, there is nothing in the Hyttinen *et al.*, reference that would motivate a skilled artisan to produce fusion proteins in which the enzyme portion is in a biologically active state. In fact, it actually teaches that producing expression of a fully active enzyme portion is unfavorable. For this reason the Hyttinen et al., citation is respectfully not available or appropriate for combination with Copley et al.

It is also important to note that as was indicated by the Court of Appeals for the Federal Circuit in EWP Corp. v. Reliance Universal, Inc., 755 F.2d 898,907, 225 USPQ 20, 25 (Fed. Cir.), cert. denied, 474 U.S. 843(1985), a reference must be considered for everything it teaches by way of technology and is not limited to the particular invention it is describing and attempting

to protect. Likewise, a reference **must** be evaluated for all its teachings and is not limited to its specific embodiments. In re Bode, 550 F.2d 656,661, 193 USPQ 12, 17 (CCPA 1977); In re Snow, 471 F.2d 1400,1403, 176 USPQ 328, 329 (CCPA 1973). The point relevant to the current discussion is that combinations of teachings from two disparate references simply may not be possible because in the effort to do so fundamental teachings of the individual citations are discarded in a way no reasonable worker in the field would consider. Each citation cited by the Examiner encompasses a certain way of doing things, a pathway with an expected outcome. To take features of a citation out of context in an effort to match them to the limitations of the current claim ignores the basic or specific innovations of the underlying references. In the current case this means that the teachings of Hyttinen et al. about the specific production of a biologically inactive molecule cannot be and should not be ignored.

Thus, it is clear that neither Hyttinen et al. nor Copley et al., alone or in combination, teach or suggest the claimed invention. Moreover, there is nothing in either of these references which would motivate a skilled artisan to combine the teachings of these references to arrive at the claimed invention. Lastly, the expression levels of the fusion protein obtained in the milk of transgenic mammals, and presently claimed, were unexpected in view of the very low expression levels of these proteins in other expression systems as presented in the cited prior art. Therefore, the Hyttinen et al. and Copley et al. references do not render the claimed invention obvious, and Applicants respectfully request that the Examiner withdraw this rejection.

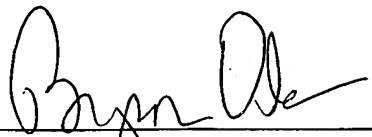
The Commissioner is authorized to charge any fee which may now or hereafter be due for this divisional application to GTC Biotherapeutics' Deposit Account No. 502092.

Applicants respectfully submit that the pending claim of this application is in condition for allowance and such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below.

Early and favorable action is earnestly solicited.

Date: 2/8/05

Respectfully Submitted,

By: 

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